V. RESULTS

A. Single-Dose Fasting Study

Within-Study Validation

		Conc., ng/mL	CV, %	%Diff.
Std. Curve;	n=28	2.00	5.8	- 12.5
	n=28	3.99	3.3	+ 4.8
	n=27	34.95	2.6	+12.8
	n=28	99.86	3.8	- 8.7
	n=28	349.50	2.6	+ 4.2
	n=27	499.29	2.4	+1.7
	n=28	599.15	2.4	+1.1
	n=28	699.01	2.1	- 0.4
	n=28	838.81	2.1	- 1.9
	n=28	1048.51	1.7	- 0.6
QC Samples;	n=56	4.99	4.5	+6.1
	n=54	299.57	2.8	+1.3
	n=55	798.87	2.3	+7.2

1. **Blood/Plasma Drug Concentration:** The mean plasma concentration data are given in Table 5, and graphic profiles are shown in Attachment 3.

2. **Pharmacokinetic Parameters**: Mean PK parameters and statistical analysis are given in Tables 6-7. Individual data are shown in Attachments 4-5.

- The 90% CI for LAUCs are within 80-125% as required (Tables 7).

- ANOVA analysis showed no significant treatment or sequence effects on AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, there was a significant period effect on AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, and $LAUC_{0-inf}$. The LS mean for Period 2 was 10.5% higher than for Period 1.

- Individual Test/Reference ratios for AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and T_{half} averaged between 0.97 and 1.07.

- The ratios of AUC_{0-t}/AUC_{0-inf} averaged 96%.

- None of the subjects had C_{max} at first non-zero time point.
- Plasma concentration-time profiles were checked for all subjects. $AUC_{0-\infty}$ was obtained correctly for all subjects.

3. Adverse Reaction: No significant differences between test and reference were observed (See the table below).

	No. Of Subjects		
Sign/Symptom	**Test**	**Reference**	**Drug Related**
Nausea	2	1	Possible/Probable
Headache	1	0	Unrelated
Stomach upset	1	3	Possible/Probable
Loose Stool	1	1	Possible/Probable
Dizziness	1	1	Possible/Probable
Appetite Loss	1	0	Possible/Probable
Trembling Feet	0	1	Possible/Probable
Insomnia	0	1	Unrelated

Conclusion: The *in vivo* fasting study is acceptable.

TABLE 5. MEAN PLASMA TICLOPIDINE HYDROCHLORIDE LEVELS FOR TEST AND REFERENCE PRODUCTS
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)
(n=45)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	35.14	51.25	22.64	64.98	1.55
1	243.53	183.83	189.67	214.71	1.28
1.33	408.99	246.49	368.75	266.09	1.11
1.67	492.98	271.15	472.28	270.65	1.04
2	466.54	262.41	463.67	251.56	1.01
2.33	360.39	237.01	380.01	242.09	0.95
2.67	284.47	204.79	325.94	234.79	0.87
3	224.53	173.71	247.87	189.11	0.91
3.5	167.33	145.60	180.04	157.09	0.93
4	122.86	105.35	128.59	105.27	0.96
6	49.10	34.65	53.15	42.90	0.92
8	32.12	22.53	33.41	27.00	0.96
12	18.25	11.39	19.08	13.26	0.96
16	11.77	7.17	11.50	7.02	1.02
24	7.40	4.35	7.53	4.75	0.98
36	4.22	3.39	4.41	3.59	0.96
48	2.47	2.39	2.61	2.71	0.95
72	1.05	1.66	1.09	1.68	0.96
96	0.24	0.80	0.35	0.91	0.69

1=TEST, 2=REFERENCE

TABLE 6. TEST MEAN/REFERENCE MEAN RATIOS (n=45; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1683.84	1019.32	1714.11	1092.42	0.98
AUCT	1631.00	988.14	1650.42	1069.44	0.99
CMAX	578.01	282.37	566.52	276.52	1.02
KE	0.06	0.03	0.05	0.03	1.06
LAUCI	1435.16	0.57	1438.76	0.60	1.00
LAUCT	1387.41	0.57	1378.57	0.61	1.01
LCMAX	514.55	0.50	505.79	0.49	1.02
THALF	16.29	8.00	16.79	7.64	0.97
TMAX	1.71	0.39	1.84	0.44	0.93

1=TEST, 2=REFERENCE

TABLE 7. LSMEANS AND 90% CONFIDENCE INTERVALS (n=45)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1687.02	1703.70	0.99	93.41	104.64
AUCT	1631.44	1640.01	0.99	93.82	105.13
CMAX	577.75	563.76	1.02	95.78	109.18
LAUCI	1445.43	1433.88	1.01	94.96	107.01
LAUCT	1389.44	1373.54	1.01	95.24	107.45
LCMAX	515.44	504.51	1.02	94.44	110.53

1=TEST 2=REFERENCE

B. Limited Food Study

Within-Study Validation

		Conc., ng/mL	CV, %	%Diff.
Std. Curve;	n=26	2.00	7.4	- 13.3
	n=25	3.99	3.8	+ 6.7
	n=25	34.95	4.6	+11.7
	n=24	99.86	4.4	- 7.6
	n=25	349.50	4.1	+ 3.0
	n=26	499.29	3.1	+0.4
	n=26	599.15	2.3	+0.9
	n=26	699.01	2.8	- 0.3
	n=26	838.81	2.6	- 0.3
	n=26	1048.51	4.2	- 1.0
QC Samples;	n=50	4.99	5.3	+5.4
	n=51	299.57	3.3	+1.2
	n=48	798.87	2.3	+6.5

A total of 24 subjects participated and completed the study successfully.

1. Blood/Plasma Drug Concentration

The average plasma concentration data, test/reference ratios, and plasma profiles are given in Tables 8-9 and Attachment-6. T/R (food) ratios during 1-24 hours are 0.7-1.8, and generally food did not change the drug plasma concentration.

2. Pharmacokinetic Parameters

- Average pharmacokinetic parameters and test/reference (food) ratios are given in Tables 10-12.
- The ratios of average test/reference (food) for AUCs and C_{max} are within 0.8-1.2 as required (Table 11).
- ANOVA analysis showed no significant period or sequence effects on AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}.
- Individual PK parameters are given in Attachments 7-9.

- Food generally showed no significant effects on C_{max}, T_{max} and AUCs, and it decreases T_{half}.
- None of the subjects had C_{max} at first non-zero time point.
- Plasma concentration-time profiles were checked for all subjects. $AUC_{0-\infty}$ was obtained correctly for all subjects.

C. Adverse Reaction: No significant differences between test and reference were observed (See the table below).

	No. Of Subjects			
Sign/Symptom	**Test (A)** Fast	**Test (B)** Fed	**Reference (C)** Fed	**Drug Related**
Dizziness	1	0	0	Possible/Probable
Fatigue	0	2	1	Unrelated
Headache	0	2	1	Unrelated
Nausea	0	1	0	Possible/Probable
Burning GI	0	1	0	Possible/Probable
Burping	0	1	0	Possible/Probable
Loose Stool	0	0	0	Possible/Probable
Vomiting	0	0	1	Possible/Probable
Sweating	0	0	1	Possible/Probable

Conclusion: The non-fasting *in vivo* study is acceptable.

VI. FORMULATION

Table 13. shows the composition of 250 mg ticlopidine hydrochloride tablets manufactured by Purepac.

TABLE 8. MEAN PLASMA Ticlopidine hydrochloride LEVELS FOR TEST AND REFERENCE PRODUCTS (N=24)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3
TIME HR					
0	0.00	0.00	0.00	0.00	0.00
0.5	62.71	119.71	26.12	57.12	82.84
1	383.07	436.57	219.39	372.13	372.40
1.33	440.54	328.87	359.47	372.58	505.64
1.67	453.81	267.09	435.41	323.07	547.53
2	376.07	230.71	473.55	250.84	473.33
2.33	336.14	191.15	439.73	280.01	366.08
2.67	280.78	162.13	382.98	278.55	288.92
3	238.66	135.90	329.90	224.23	222.36
3.5	178.21	103.01	256.91	187.14	147.97
4	139.20	86.36	201.11	153.26	119.30
6	54.68	34.68	67.35	39.68	45.56
8	32.10	17.26	38.95	22.13	32.13
12	18.68	9.03	21.26	11.33	18.41
16	13.35	6.54	14.79	7.70	13.43
24	9.07	4.71	9.94	4.90	8.59
36	5.50	3.75	6.26	4.01	4.97
48	3.61	3.00	3.92	2.90	3.19
72	1.51	1.74	2.00	1.86	1.44
96	0.92	1.24	1.02	1.39	0.60

1=TEST FED 2=REFERENCE FED, 3=TEST FASTING

TABLE 9. RATIO OF TEST/REFERENCE MEAN PLASMA Ticlopidine hydrochloride LEVELS (N=24)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR				
0	0.00	.	.	.
0.5	136.23	2.40	0.76	0.32
1	347.77	1.75	1.03	0.59
1.33	316.38	1.23	0.87	0.71
1.67	269.20	1.04	0.83	0.80
2	222.49	0.79	0.79	1.00
2.33	206.29	0.76	0.92	1.20
2.67	172.26	0.73	0.97	1.33
3	143.58	0.72	1.07	1.48
3.5	87.64	0.69	1.20	1.74
4	75.43	0.69	1.17	1.69
6	25.10	0.81	1.20	1.48
8	16.65	0.82	1.00	1.21
12	9.34	0.88	1.01	1.15
16	7.05	0.90	0.99	1.10
24	4.62	0.91	1.06	1.16
36	3.26	0.88	1.11	1.26
48	2.46	0.92	1.13	1.23
72	1.81	0.76	1.05	1.39
96	1.20	0.91	1.54	1.70

1=TEST FED 2=REFERENCE FED, 3=TEST FASTING

TABLE 10. TEST MEAN/REFERENCE MEAN (n=24; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	1869.44	974.29	2183.31	1074.17	1869.22
AUCT	1796.01	953.21	2033.78	1057.98	1802.10
CMAX	610.35	371.31	672.16	337.23	636.72
KE	0.04	0.02	0.04	0.02	0.05
LAUCI	1605.68	0.59	1874.95	0.61	1562.74
LAUCT	1532.65	0.61	1715.10	0.65	1512.80
LCMAX	515.12	0.60	575.66	0.62	560.52
THALF	19.24	8.40	22.75	9.57	18.20
TMAX	1.62	0.58	2.07	1.08	1.56

1=TEST FED 2=REFERENCE FED 3=TEST FASTING (CONTINUED)

TABLE 11. TEST MEAN/REFERENCE MEAN RATIOS (n=24; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	1004.35	0.86	1.00	1.17
AUCT	952.87	0.88	1.00	1.13
CMAX	299.94	0.91	0.96	1.06
KE	0.03	1.17	0.87	0.75
LAUCI	0.67	0.86	1.03	1.20
LAUCT	0.66	0.89	1.01	1.13
LCMAX	0.55	0.89	0.92	1.03
THALF	9.41	0.85	1.06	1.25
TMAX	0.32	0.78	1.04	1.33

TABLE 12. LSMEANS AND RATIOS (n=24)

	LSM1	LSM2	LSM3	RLSM12	RLSM13
PARAMETER					
AUCI	1869.44	2127.43	1888.33	0.88	0.99
AUCT	1796.01	2033.78	1802.10	0.88	1.00
CMAX	610.35	672.16	636.72	0.91	0.96
LAUCI	1605.68	1782.42	1587.63	0.90	1.01
LAUCT	1532.65	1715.10	1512.80	0.89	1.01
LCMAX	515.12	575.66	560.52	0.89	0.92

(CONTINUED)

	RLSM23
PARAMETER	
AUCI	1.13
AUCT	1.13
CMAX	1.06
LAUCI	1.12
LAUCT	1.13
LCMAX	1.03

1=TEST FED 2=REFERENCE FED 3=TEST FASTING

VII. *IN VITRO* RESULTS (DISSOLUTION):

There is no USP method available. One study was approved with water as the dissolution medium. The firm has used old FDA method, which recommended 0.1 N HCl as well as water as medium (Table 14). Dissolution profiles are similar in both media. The product passes the dissolution specification of

TABLE 14. *In Vitro* Dissolution Testing

A. Conditions

Method, Apparatus II (Paddle) **RPM: 50** **No. of Units: 12**
Medium: 0.1 N HCl/Water **Volume:** 900 mL
Reference Drug: Ticlid[R] **Manufacturer:** Syntex (Roche)
Assay Methodology:

B. Results

Sampling Time (Minutes)	Test Product Mean % Dissol.	Range	CV	Reference Product Mean % Dissol.	Range	CV
Medium: 0.1N HCl	**Lot #PI-997**		**Strength 250 mg**		**Lot # 07635A**	
10	82.4		4.5	84.5		8.5
20	93.5		3.0	90.4		6.1
30	95.9		1.9	91.9		4.9
45	96.7		1.4	93.3		4.0
60	97.0		1.2	94.1		3.4
Medium: Water (see Submissioin dated 4/6/98)						
10	83.9		3.9	83.1		9.8
20	96.3		1.5	94.4		5.3
30	98.8	2	1.6	97.5		4.2
45	99.7	2	1.6	99.0		3.6
60	100.1	3	1.7	99.5	3	3.2

VIII. DEFICIENCY

None

IX. RECOMMENDATION

1. The *in vivo* bioequivalence study conducted under fasting conditions by Purepac on its ticlopidine hydrochloride tablets, 250 mg strength, Lot #PI997, comparing it to Roche's 250 mg strength Ticlid[R] tablets, 250 mg strength, Lot #07635A, has been found acceptable by the Division of Bioequivalence.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Purepac on its ticlopidine hydrochloride tablets, 250 mg strength, Lot #PI997, comparing it to Roche's Ticlid[R] tablets, 250 mg strength, Lot #07635A, has been found acceptable by the Division of Bioequivalence.

3. The dissolution testing conducted by Purepac, on its ticlopidine hydrochloride250 mg, Lot #PI997 is acceptable.

   The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37 °C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

4. From the bioequivalence point of view, the firm has met the in vivo bioavailability and *in vitro* dissolution testing requirements for its ticlopidine hydrochloride ıg tablets, and the application is acceptable.

The firm should be informed of the recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar

/S/ 4/7/1998

Concur: /S/ Date: 4/8/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Attachments-9

SPS/sps/3-17-98/75253SDW.N97

BIOEQUIVALENCY COMMENTS

ANDA: 75-253 APPLICANT: Purepac Pharmaceutical Co.

DRUG PRODUCT: Ticlopidine Hydrochloride Tablets, 250 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water, at 37 °C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:

X:NEW\FIRMSNZ\Purepac\ltrs&rev\75253SD.N97
Printed in final on 3/18/98

Endorsements: (Final with Dates)
HFD-650/ SShrivastava 4/7/98
HFD-655/ SNerurkar
HFD-617/ L. Sanchez or N. Chamberlin
HFD-650/ D. Conner 4/8/98

BIOEQUIVALENCY - UNACCEPTABLE

1. **FASTING STUDY** (STF) — Strengths: 250 mg
   Clinical:
   Analytical — **Outcome: AC**

2. **FOOD STUDY** (STP) — Strengths: 250 mg
   Clinical:
   Analytical — **Outcome: AC**

3. **DISSOLUTION DATA** (DIS) — All Strengths
   April 6, 98 — Outcome: **AC**

Outcome Decisions:
AC - Acceptable

WINBIO COMMENTS:

3 Dissolution Data (Dis) All AC
April 6, 98

Table 13. Composition of Purepac's Ticlopidine Hydrochloride Tablets

Ingredient	**mg/Tablet**
Tablet Core	**Test**
Ticlopidine hydrochloride	250.0
Lactose monohydrate,	
Hydroxypropyl cellulose,	
Microcrystalline cellulose,	
Crospovidone,	
Colloidal silicone dioxide,	
Calcium Stearate,	
Total Core Weight	
Film Coating	
Purified water	
Total Tablet Weight	**414.0**

*This component does not appear in significant quantity in the finished product.